

Internal Medicine Research Review

Making Education Easy

Issue 13 - 2009

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Welcome to issue 13 of Internal Medicine Research Review.

Among this selection of papers relevant to internal medicine, we take look at the possible drug-drug interactions that involve the main ingredients of 'party pills', and we learn that tamsulosin received within 14 days of cataract surgery increases the risk of serious postoperative ophthalmic adverse effects. An RCT has shown that single IV zoledronic acid infusions seem to be better than daily oral risedronate for preventing and treating glucocorticoid-induced osteoporosis, and are usually preferred by patients.

We hope you enjoy this Review, and we welcome your feedback.

Kind regards,

Dr Chris Tofield

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Larval therapy for leg ulcers (VenUS II)

Authors: Dunville JC et al

Summary: The clinical efficacy of loose or bagged larval therapy was compared with a standard debridement therapy (hydrogel) in this RCT of 267 patients with ≥ 1 venous or mixed venous/arterial leg ulcer with $\geq 25\%$ coverage of slough or necrotic tissue, and an ankle brachial pressure index ≥ 0.6 . Time to healing of largest eligible ulcer (primary endpoint) did not differ significantly among the treatment groups. Larval therapy was associated with a significantly reduced time to debridement (hazard ratio 2.31; 95% CI 1.65, 3.2), but was also associated with higher ulcer-related pain scores. Health-related quality of life, change in bacterial load and ability to eradicate MRSA did not differ significantly among the groups, although the analysis of the latter was underpowered.

Comment: Chronic leg ulcers are an important but often neglected public health problem. This underpowered study looked at effectiveness of two forms of larval therapy compared with hydrogel in treatment of sloughy and necrotic leg ulcers. The ulcers took a long time to heal and there was little difference among treatments. More interdisciplinary studies are required in this important area of medicine to optimise patient outcomes.

Reference: *BMJ* 2009; 338: b773

http://www.bmj.com/cgi/content/full/338/mar19_2/b773

*Independent commentary by Dr Sisira Jayathissa,
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Party pills and drug-drug interactions

Authors: Murphy M et al

Summary: Interactions between drugs commonly used in the clinical setting and drugs contained in party pills, benzylpiperazine (BZP) and trifluoromethylphenylpiperazine (TFMPP), were investigated using pooled human liver microsomes. The metabolism of caffeine (CYP1A2 substrate), dextromethorphan (CYP2D6 substrates) and ethinylestradiol (CYP3A4), but not omeprazole (CYP2C19 substrate) were inhibited by both BZP and TFMPP. Enzyme inhibition was greater with TFMPP than BZP.

Comment: This small study highlights the potential for interactions between commonly used party pills and substances metabolised by CYP2D6 and to a lesser extent by CYP3A4 and CYP2C19. Clinical relevance of this study is not very clear. However, it emphasises the importance of taking a detailed medication history, including consumption of party pills, when a patient presents with atypical symptoms.

Reference: *NZ Med J* 2009; 122(1293): 26–35
<http://www.nzma.org.nz/journal/abstract.php?id=3564>

Surgical decompression for space-occupying cerebral infarction (HAMLET)

Authors: Hofmeijer J et al

Summary: In this study, 64 patients with space-occupying hemispheric infarction were randomly assigned to surgical decompression within 4 days of stroke onset or best medical treatment. Modified Rankin scale score at 1 year (primary outcome) did not differ between the two treatment groups, but case fatality decreased by 38% with surgical decompression. When data from the patients who underwent surgical decompression within 48 hours of stroke onset were combined with those from the DECIMAL and DESTINY studies in a meta-analysis, surgical decompression reduced poor outcome and case fatality risks by 16% and 50%, respectively.

Comment: Large MCA infarcts with cerebral oedema often lead to poor clinical outcomes. Previous studies have shown beneficial effects of early decompressive surgery. This underpowered small study suggests lack of functional and survival benefits if surgery is offered within 4 days of onset. However, subgroup analysis of patients undergoing surgery within 48 hours together with pooled data from two other small randomised trials show significant survival and functional benefits, but poor quality of life. Stroke units should consider developing protocols to promptly diagnose and manage patients with malignant MCA syndrome.

Reference: *Lancet Neurol* 2009; 8(4): 326–33
[http://www.thelancet.com/journals/lanneur/article/PIIS1474-4422\(09\)70047-X/abstract](http://www.thelancet.com/journals/lanneur/article/PIIS1474-4422(09)70047-X/abstract)

The Paracetamol (Acetaminophen) In Stroke (PAIS) trial

Authors: den Hertog HM et al

Summary: Participants in this RCT (n=1400) were randomised to receive paracetamol (acetaminophen) 6 g/day or placebo within 12 hours of the onset of symptoms associated with ischaemic stroke or intracerebral haemorrhage to investigate if lowering body temperature improves outcomes. Improvements were not significantly different between the paracetamol and placebo groups (37% vs. 33%), but in a post-hoc analysis, paracetamol was associated with an improved outcome among patients with a baseline body temperature of 37–39°C (odds ratio 1.43; 95% CI 1.02, 1.97). The investigators concluded routine use of high-dose paracetamol is not supported by these data, and further studies investigating benefits in patients with body temperatures 37–39°C at admission are needed.

Comment: High body temperature is known to be associated with poor prognosis in stroke patients. In this large but underpowered study, administration of oral paracetamol up to 6 g/day compared with placebo in patients with mild-to-moderately severe stroke did not improve the clinical outcomes. There was a high dropout rate. In a post-hoc analysis, patients with body temperature between 37–39°C benefited from treatment. Routine use of paracetamol is not recommended for all strokes, but could become a standard practice for patients with body temperatures between 37 and 39°C.

Reference: *Lancet Neurol* 2009; 8(5): 434–40
[http://www.thelancet.com/journals/lanneur/article/PIIS1474-4422\(09\)70051-1/abstract](http://www.thelancet.com/journals/lanneur/article/PIIS1474-4422(09)70051-1/abstract)

Zoledronic acid and risedronate in the prevention and treatment of glucocorticoid-induced osteoporosis (HORIZON)

Authors: Reid DM et al

Summary: This noninferiority, randomised study compared the efficacy of one IV infusion of zoledronic acid 5mg (n=416) with oral risedronate 5 mg/day (417) for the prevention/treatment of glucocorticoid-induced osteoporosis; 62 patients dropped out. Zoledronic acid recipients experienced a greater increase in lumbar spine bone mineral density than risedronate recipients in both treatment (>3 months' treatment) and prevention analyses (<3 months' treatment; mean differences at 12 months +1.36%; 95% CI 0.67, 2.05; p=0.0001, and +1.96%; 1.04, 2.88; p<0.0001, respectively), demonstrating noninferiority and superiority of zoledronic acid. Zoledronic acid recipients experienced more adverse effects, although these were largely due to transient symptoms occurring within 3 days of the infusion.

Comment: Zoledronic acid is more potent than risedronate and as expected showed a superior improvement in BMD. There was no difference in the occurrence of vertebral fractures. Patients preferred zoledronic acid compared with risedronate. A longer study may have shown superior clinical outcomes, but also adverse effects such as osteonecrosis. Longer term safety data need to be considered when selecting a suitable bisphosphonate for managing steroid-induced osteoporosis in this relatively young group of patients, especially if long-term steroid treatment is planned.

Reference: *Lancet* 2009; 373(9671): 1253–63
[http://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(09\)60250-6/fulltext](http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(09)60250-6/fulltext)

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Relaxin for the treatment of patients with acute heart failure (Pre-RELAX-AHF)

Authors: Teerlink JR

Summary: Patients with acute heart failure, dyspnoea, congestion on chest x-ray, increased brain natriuretic peptide (BNP) or N-terminal prohormone of BNP levels, mild-to-moderate renal insufficiency and systolic BP >125mm Hg (n=234) were randomised to receive relaxin 10 µg/kg, 30 µg/kg, 100 µg/kg or 250 µg/kg, or placebo with standard care in this dose-finding phase IIb RCT. Findings included: 1) moderate-to-marked dyspnoea improvement (Likert scale) with relaxin 30 µg/kg compared with placebo (40% vs. 23% of patients; p=0.044); 2) shorter hospital stay in relaxin groups (10.2 vs. 12.0 days); 3) longer time alive out of hospital in relaxin groups (47.9 vs. 44.2 days); 4) lower rate of cardiovascular mortality and 60-day readmission for heart or renal failure in relaxin groups (2.6% vs. 17.2%); and 5) similar between-group numbers of serious adverse events.

Comment: Little progress has been made in the treatment of acute heart failure in spite of advances in medical science. This phase II study suggests some benefits of relaxin, a naturally occurring peptide, in the management of acute heart failure. The sample size is too small to draw definite conclusions, but planned larger phase III trials may help to establish its place in the management of acute heart failure in a less selective population.

Reference: *Lancet* 2009; 373(9673): 1429-39

<http://tinyurl.com/Lancet-373-1429>

Efficacy of esomeprazole for treatment of poorly controlled asthma

Authors: The American Lung Association Asthma Clinical Research Centers

Summary: This study showed that patients with poorly controlled asthma and with minimal or no gastro-oesophageal reflux symptoms who were randomised to receive esomeprazole 40mg twice daily for 24 weeks had a similar frequency of poor asthma control episodes (primary outcome) as those who received placebo. Similarly, the active treatment was not associated with any improvements in the individual components of the primary outcome or any of the secondary outcomes measured. There were also no benefits seen in the subgroup of patients with gastro-oesophageal reflux.

Comment: The role of gastro-oesophageal reflux in the development or persistence of asthma symptoms is not known, but PPIs are used in patients with nocturnal asthma symptoms. In this well-conducted RCT, high-dose PPI therapy didn't improve asthma control of patients without symptoms of gastro-oesophageal reflux disease. A significant number of participants had asymptomatic reflux. Routine use of PPI in the treatment of nocturnal asthma without symptomatic reflux disease is not recommended.

Reference: *N Engl J Med* 2009; 360(15): 1487-99

<http://content.nejm.org/cgi/content/abstract/360/15/1487>

Rosuvastatin and cardiovascular events in patients undergoing hemodialysis

Authors: Fellström BC et al

Summary: The benefits of an HMG-CoA reductase inhibitor (statin) on cardiovascular (CV) events was investigated in 2776 high CV-risk patients, aged 50-80 years, undergoing haemodialysis. Patients randomly assigned to receive rosuvastatin 10 mg/day had a similar rate of the combined primary endpoint (death from CV causes, nonfatal myocardial infarction and vascular events) after a mean follow-up period of 3.8 years as those randomised to receive placebo (hazard ratio 0.96; 95% CI 0.84, 1.11). Similarly, there were no benefits in the rosuvastatin group for any of the components of the primary endpoint or for the all-cause mortality rate.

Comment: Haemodialysis is associated with high mortality. Approximately half of the patients randomised died during 3.8 years of follow up. As in the 4D trial, there was no improvement in hard endpoints with statin therapy in spite of a marked reduction in cholesterol level, indicating that cholesterol is not a good surrogate for predicting CV outcomes in haemodialysis patients. Routine use of statins in patients undergoing haemodialysis is not recommended.

Reference: *N Engl J Med* 2009; 360(14): 1395-407

<http://content.nejm.org/cgi/content/abstract/360/14/1395>

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Association between tamsulosin and serious ophthalmic adverse events in older men following cataract surgery

Authors: Bell CM et al

Summary: Tamsulosin-associated ophthalmic risks following cataract surgery were retrospectively explored in 96,128 men aged ≥ 66 years who were receiving the agent for benign prostatic hypertrophy (BPH). Among the 284 (0.3%) participants who experienced an ophthalmic adverse event (retinal detachment, lost lens or lens fragment, or endophthalmitis), these were significantly more frequent among patients who had received tamsulosin ≤ 14 days after cataract surgery (estimated number needed to harm 255), than those who received the agent > 15 days after surgery or those with any exposure to other α -blockers.

Comment: Previous use of tamsulosin is known to cause floppy iris syndrome during cataract surgery. This large observational study suggests an increased incidence of other postoperative complications following cataract surgery associated with the use of tamsulosin, but not other α -blockers. All practitioners involved in the care of older patients taking tamsulosin for BPH and coming for cataract surgery need to be aware of these complications so appropriate actions can be taken to reduce adverse outcomes.

Reference: *JAMA* 2009; 301(19): 1991–6

<http://jama.ama-assn.org/cgi/content/full/301/19/1991>

Meat intake and mortality: a prospective study of over half a million people

Authors: Sinha R et al

Summary: This analysis investigated the relationship between meat consumption and mortality using data from a cohort of $> 500,000$ individuals, among whom there were 47,976 and 23,276 deaths in males and females, respectively, during 10 years of follow-up. The risk of mortality from any cause was greater among individuals in the highest quintiles of red and processed meat consumption than it was among those in the lowest quintiles (hazard ratios 1.31; 95% CI 1.27, 1.35 and 1.36; 1.30, 1.43, respectively). Those in the highest quintiles also had elevated risks of cancer mortality and cardiovascular disease. An inverse association was identified for both total and cancer mortalities when the highest and lowest quintiles of white meat consumption were compared.

Comment: This interesting observational study indicates an increased incidence of adverse health outcomes with a high intake of red or processed meat. The causal association is not clear, but is likely to be multifactorial. There was no information provided with hazards associated with vegetarian or fish-based diets. Studies looking at diets are tainted with multiple confounders, but large studies like this may help in our understanding of good and bad ingredients in our diet.

Reference: *Arch Intern Med* 2009; 169(6): 562–71

<http://archinte.ama-assn.org/cgi/content/abstract/169/6/562>

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Residual thrombosis on ultrasonography to guide the duration of anticoagulation in patients with deep venous thrombosis

Authors: Prandoni P et al

Summary: The effect of adjusting the duration of anticoagulation therapy based on residual thrombi was investigated in 538 patients with a first episode of acute proximal deep vein thrombosis (DVT) who had received 3 months of anticoagulation therapy without incident. The participants were randomised to receive flexible-duration anticoagulation (≤ 21 months and ≤ 9 months for unprovoked and secondary DVT, respectively), and none for patients with recanalised veins) or fixed-duration anticoagulation (3 months and none for unprovoked and secondary DVT, respectively). The rate of confirmed recurrent DVT during 33 months of follow up was significantly lower for the flexible-duration group than the fixed-duration group (11.9% vs. 17.2%; hazard ratio 0.64; 95% CI 0.39, 0.99). The adjusted hazard ratios for unprovoked and secondary DVT were 0.61 (95% CI 0.36, 1.02) and 0.81 (0.32, 2.06), respectively. The rates of major bleeding were not significantly different between the flexible- and fixed-duration groups (1.5% and 0.7%, respectively).

Comment: Venous thromboembolism is increasingly recognised as a chronic disease. Measurements such as D-dimer and ultrasound evidence for recanalisation have been used to determine the optimum duration of anticoagulation therapy. This study of patients with a first proximal DVT suggests benefits of repeat leg ultrasound in determining the optimal duration of anticoagulation. Appropriate measures to improve treatment effectiveness are needed to maximise the treatment benefits and reduce the complications associated with long-term warfarin therapy.

Reference: *Ann Intern Med* 2009; 150(9): 577–85

<http://www.annals.org/cgi/content/abstract/150/9/577>

Effect of clopidogrel added to aspirin in patients with atrial fibrillation

Authors: The ACTIVE Investigators

Summary: The addition of clopidogrel to aspirin for reducing the risk of vascular effects in 7554 patients with atrial fibrillation and an increased risk of stroke, but who were unsuitable for vitamin K therapy, was explored in this study. The primary outcome (composite of stroke, myocardial infarction, non-CNS embolism or death from vascular causes) occurred in less participants who were randomised to receive aspirin with clopidogrel 72mg than in those who received aspirin with placebo (6.8% vs. 7.6% per year; relative risk 0.89; 95% CI 0.81, 0.98; $p=0.01$); stroke was the main contributor to the difference (2.4% vs. 3.3% per year; 0.72; 0.62, 0.83; $p<0.001$) and the rates of myocardial infarction were 0.7% vs. 0.9% per year (relative risk 0.78; 0.59, 1.03; $p=0.08$). The yearly rates of major bleeding were 2.0% and 1.3% of aspirin/clopidogrel and aspirin/placebo recipients, respectively (relative risk 1.57; 95% CI 1.29, 1.92; $p<0.001$).

Comment: This large RCT showed a superior benefit in stroke prevention of clopidogrel plus aspirin compared with aspirin alone in patients with atrial fibrillation (NNT 112). However, this benefit was associated with an increased risk of major bleeding (NNH 143). There was a very high rate of discontinuation of clopidogrel and placebo compared with aspirin. Warfarin should be the first-line treatment for stroke prevention in patients with atrial fibrillation, and the combination of clopidogrel and aspirin should be considered on a case-by-case basis based on the magnitude of the potential benefit versus harm.

Reference: *N Engl J Med* 2009; 360(20): 2066–78

<http://content.nejm.org/cgi/content/abstract/360/20/2066>

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